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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 2002.010 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/07477	International filing date *(day/month/year)* 09.07.2003	Priority date *(day/month/year)* 10.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/012		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.02.2004	23.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Noë, V Telephone No. +31 70 340-4181

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07477

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-30 as originally filed

Claims, Numbers

1-14 as originally filed

Drawings, Sheets

1-3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

V. Reasoned statement (Continuation)

1 CITATIONS

Reference is made to the following documents:

D1: ARMAH G E ET AL: "CONFORMATION AND IMMUNOGENICITY OF ENGINEERED REPEATING SEGMENT OF THE CIRCUMSPOROZOITE SURFACE PROTEIN OF PLASMODIUM-FALCIPARUM" MOLECULAR AND BIOCHEMICAL PARASITOLOGY, vol. 38, no. 1, 1990, pages 135-140, XP008015832 ISSN: 0166-6851

D2: CARCY B ET AL: "A 37-kilodalton glycoprotein of Babesia divergens is a major component of a protective fraction containing low-molecular-mass culture-derived exoantigens" INFECTION AND IMMUNITY, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, US, vol. 63, no. 3, March 1995 (1995-03), pages 811-817, XP002116987 ISSN: 0019-9567

D3: WO 89/01041 A (GENENTECH INC) 9 February 1989 (1989-02-09)

2 NOVELTY (Art. 33(2) PCT)

2.1 The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of claims is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

3 INVENTIVE STEP (Art. 33(3) PCT)

3.1 Document D1 is considered to represent the most relevant state of the art and discloses a vaccine composition comprising a fusion protein of a immunodominant tetrapeptide repeat of the circumsporozoite surface protein of Plasmodium falciparum N-terminally fused to a hydrophobic protein (human growth hormone) and Freunds complete adjuvant. The use of the fusion protein results in a higher antigenicity and in this way an optimal immune response of can be obtained (see abstract; page 135, column 2, line 17 - page 136, column 1, first paragraph; figure 1; page 137, column 1, last paragraph - column 2, first paragraph; page 138, column 2, line 10 - page 139). The subject-matter of claims 1-4,9,10 differs in that

a vaccine composition comprising a fusion protein comprising a heterologous more hydrophobic peptide and a saponin adjuvant in free form is claimed.

3.2 The problem to be solved by the subject matter of claim 1 may therefore be regarded as the provision of an alternative vaccine. The solution would be a vaccine composition comprising a fusion protein comprising a heterologous more hydrophobic peptide and a saponin adjuvant in free form.

3.3 This solution cannot however be considered as involving an inventive step (Article 33(3) PCT) because D2 discloses the use of Quil A saponin as adjuvant in Babesia divergens vaccine composition (see abstract and page 812, column 1, paragraph 4 - column 2, paragraph 1).

3.3.1 The application mentions that the use of a combination of a fusion protein with a saponin adjuvant in free form in the claimed vaccine composition leads to reduced side effects of this adjuvant, however, in example 3 example shows the results of vaccinations with the fusion protein as claimed but also of control vaccinations (not having the fusion protein) and it is clearly stated "no significant negative local reactions were observed with the amount of Quill A (75µg/dose) that was used in these vaccinations"(see page 27, line 11-12). Therefore, the use of a saponin in free form as vaccine adjuvant is not considered to be inventive. Even in the control vaccinations no negative side effects of the adjuvant were observed, indicating that the reduction of side effects is not due to the combination of the fusion protein and the adjuvant.

3.3.2 The use of another fusion protein comprising a heterologous more hydrophobic peptide to improve the immune response is not considered to be inventive because it would be obvious for the person skilled in the art. D1 shows that fusion of even a less hydrophobic peptide to the an antigen results in higher antigenicity, therefore, the skilled person would consider the use of other even more hydrophobic peptides for making the fusion protein of the present application. Although the application mentions that a hydrophobic peptide must at least have 60% of hydrophobic data points, the application does not show that proteins being less hydrophobic do not have this effect.

3.4 Therefore the subject-matter of claims 1-4, 9,10 does not involve an inventive step.

3.5 Dependent claims 5-7 do not appear to contain any additional features which, in

combination with the features of any claim to which they refer, involve an inventive step because D1 discloses the fusion of a immunogenic peptide with a hydrophobic protein, human growth hormone, being hydrophobic over the whole sequence (see also reasoning point 3.3.2 above).

3.6 Dependent claim 8 does not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step because D3 discloses use of the C-terminal hydrophobic sequence of DAF for making fusion proteins (see page 5, line 20-32; page 10, line 31 - page 11, line 18; page 13, line 18-26; page 15, line 21-33) and in combination with the teachings of D1, it would be obvious for the skilled person to use the C-terminal hydrophobic sequence of DAF for making fusion proteins to improve the immune response to an antigen.

3.7 Claims 11 and 12 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step because the subject-matter of these claims would be obvious for the skilled person.

3.8 Claims 13 and 14 are not considered to involve an inventive step because a method for preparation of a vaccine by admixing an immunogenic composition of claims 1-9 and a pharmaceutically acceptable carrier and the use of the immunogenic composition of claims 1-9 for the preparation of a vaccine would be obvious for the person skilled in the art.

3.9 The present application does therefore not satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims 1-14 does not involve an inventive step (Rule 65(1)(2) PCT).